

WHAT IS CLAIMED IS:

1. An isolated nucleic acid encoding an IRAK-4 polypeptide, said polypeptide having at least about 98% amino acid sequence identity to SEQ ID NO:1 or to a subsequence thereof, wherein the amino acid sequence of the polypeptide comprises an alanine residue at an amino acid position corresponding to amino acid position 81 of SEQ ID NO:1, and wherein said nucleic acid comprises at least about 400 nucleotides.

2. The nucleic acid of claim 1, wherein the polypeptide further comprises an amino acid selected from the group consisting of:

(i) a valine residue at an amino acid position corresponding to amino acid position 432 of SEQ ID NO:1;

(ii) a leucine residue at an amino acid position corresponding to amino acid position 437 of SEQ ID NO:1;

(iii) an arginine residue at an amino acid position corresponding to amino acid position 444 of SEQ ID NO:1; and

(iv) a glutamine residue at an amino acid position corresponding to amino acid position 451 of SEQ ID NO:1.

3. The nucleic acid of claim 2, wherein the polypeptide comprises each of the amino acids listed as (i) to (iv).

4. The nucleic acid of claim 1, wherein the polypeptide comprises an amino acid sequence of SEQ ID NO:1.

5. The nucleic acid of claim 1, wherein the polypeptide comprises at least about 100 amino acids.

6. The nucleic acid of claim 1, wherein the polypeptide comprises at least about 450 amino acids.

7. The nucleic acid of claim 1, wherein the nucleic acid comprises a cytosine at a nucleotide position corresponding to nucleotide position 242 of SEQ ID NO:2.

8. The nucleic acid of claim 7, wherein the nucleic acid further comprises a nucleotide selected from the group consisting of:

3 (i) a thymine at a nucleotide position corresponding to nucleotide position  
4 1295 of SEQ ID NO:2;  
5 (ii) a thymine at a nucleotide position corresponding to nucleotide position  
6 1302 of SEQ ID NO:2;  
7 (iii) a thymine at a nucleotide position corresponding to nucleotide  
8 position 1310 of SEQ ID NO:2;  
9 (iv) an adenine at a nucleotide position corresponding to nucleotide  
10 position 1332 of SEQ ID NO:2; and  
11 (v) an adenine at a nucleotide position corresponding to nucleotide  
12 position 1353 of SEQ ID NO:2.

1 9. The nucleic acid of claim 8, wherein the nucleic acid comprises  
2 each of the nucleotides listed as (i) to (v).

1 10. The nucleic acid of claim 1, wherein the nucleic acid comprises a  
2 nucleotide sequence of SEQ ID NO:2.

1 11. The nucleic acid of claim 1, wherein the nucleic acid comprises at  
2 least about 1350 nucleotides.

1 12. The nucleic acid of claim 1, wherein the polypeptide specifically  
2 binds to antibodies generated against a polypeptide comprising an amino acid sequence of  
3 SEQ ID NO:1.

1 13. The nucleic acid of claim 1, wherein the nucleic acid is operably  
2 linked to a promoter.

1 14. An expression cassette comprising the nucleic acid of claim 13.

1 15. An isolated cell comprising the expression cassette of claim 14.

1 16. An isolated IRAK-4 polypeptide, said polypeptide having at least  
2 about 98% amino acid sequence identity to SEQ ID NO:1 or to a subsequence thereof,  
3 wherein the amino acid sequence of the polypeptide comprises an alanine residue at an  
4 amino acid position corresponding to amino acid position 81 of SEQ ID NO:1, and  
5 wherein the polypeptide comprises at least about 100 amino acids.

1 17. The polypeptide of claim 16, wherein the polypeptide further  
2 comprises an amino acid selected from the group consisting of:  
3 (i) a valine residue at an amino acid position corresponding to amino acid  
4 position 432 of SEQ ID NO:1;  
5 (ii) a leucine residue at an amino acid position corresponding to amino  
6 acid position 437 of SEQ ID NO:1;  
7 (iii) an arginine residue at an amino acid position corresponding to amino  
8 acid position 444 of SEQ ID NO:1; and  
9 (iv) a glutamine residue at an amino acid position corresponding to amino  
10 acid position 451 of SEQ ID NO:1.

1 18. The polypeptide of claim 17, wherein the polypeptide comprises all  
2 of the amino acids listed as (i) to (iv).

1 19. The polypeptide of claim 16, wherein the polypeptide comprises an  
2 amino acid sequence of SEQ ID NO:1.

1 20. The polypeptide of claim 16, wherein the polypeptide is encoded  
2 by a nucleic acid comprising a nucleotide sequence of SEQ ID NO:2.

1 21. The polypeptide of claim 16, wherein the polypeptide specifically  
2 binds to antibodies generated against a polypeptide comprising an amino acid sequence of  
3 SEQ ID NO:1.

1 22. The polypeptide of claim 16, wherein the polypeptide comprises at  
2 least about 450 amino acids.

1 23. An isolated nucleic acid encoding an IRAK-4 polypeptide, said  
2 polypeptide comprising at least about 70% amino acid sequence identity to SEQ ID NO:3  
3 or to a subsequence thereof.

1 24. The nucleic acid of claim 23, wherein said polypeptide comprises  
2 an amino acid sequence of SEQ ID NO:3.

1                    25.    The nucleic acid of claim 23, wherein said nucleic acid comprises  
2    at least about 70% nucleotide sequence identity to SEQ ID NO:4 or to a subsequence  
3    thereof.

1                    26.    The nucleic acid of claim 23, wherein said nucleic acid comprises a  
2    nucleotide sequence of SEQ ID NO:4.

1                    27.    The nucleic acid of claim 23, wherein said nucleic acid hybridizes  
2    under stringent hybridization conditions to a nucleic acid comprising a nucleotide  
3    sequence of SEQ ID NO:4.

1                    28.    The nucleic acid of claim 23, wherein said nucleic acid is operably  
2    linked to a promoter.

1                    29.    An expression cassette comprising the nucleic acid of claim 28.

1                    30.    An isolated cell comprising the expression cassette of claim 29.

~~31~~ 2                    31.    A method of making an IRAK-4 polypeptide, the method  
3    comprising:

4                    (i) introducing a nucleic acid of claim 1 or claim 19 into a host cell or  
5    cellular extract;

6                    (ii) incubating said host cell or cellular extract under conditions such that  
7    said IRAK-4 polypeptide is expressed in the host cell or cellular extract; and

8                    (iii) recovering the IRAK-4 polypeptide from the host cell or cellular  
9    extract.

1                    32.    A method of identifying a compound useful in the treatment of  
2    inflammatory diseases, comprising the steps of:

3                    (i) contacting an IRAK-4 polypeptide with said compound, wherein said  
4    IRAK-4 polypeptide comprises at least about 70% amino acid sequence identity to SEQ  
5    ID NO:1 or SEQ ID NO:3; and

6                    (ii) determining the functional effect of said compound on said IRAK-4  
7    polypeptide.

1 33. The method of claim 32, wherein said IRAK-4 comprises an amino  
2 acid sequence shown as SEQ ID NO:1 or SEQ ID NO:3.

1 34. The method of claim 32, wherein the compound inhibits IRAK-4  
2 kinase activity.

1 35. The method of claim 32, wherein said IRAK-4 is present inside of  
2 a eukaryotic cell.

1 36. A method of treating an inflammatory disease in a patient, the  
2 method comprising administering to said patient a therapeutically effective amount of a  
3 compound that modulates IRAK-4.

1 37. The method of claim 36, wherein said compound inhibits IRAK-4  
2 kinase activity.

1 38. The method of claim 36, wherein said compound is identified using  
2 the method of claim 32.

1 39. The method of claim 36, wherein the inflammatory disease is  
2 selected from the group consisting of pulmonary diseases and diseases of the airway,  
3 transplant rejection, autoimmune diseases, cancer, cardiovascular diseases, diseases of the  
4 central nervous system, CD14 mediated sepsis, non-CD14 mediated sepsis, osteoarthritis,  
5 osteoporosis, psoriasis, diseases of the skin, inflammatory bowel disease, Behcet's  
6 syndrome, ankylosing spondylitis, sarcoidosis, gout, and ophthalmic diseases and  
7 conditions.

1 40. The method of claim 39, wherein the pulmonary disease and  
2 disease of the airway is selected from the group consisting of Adult Respiratory Disease  
3 Syndrome (ARDS), Chronic Obstructive Pulmonary Disease (OPD), pulmonary fibrosis,  
4 interstitial lung disease, asthma, chronic cough, and allergic rhinitis..

1 41. The method of claim 39, wherein the autoimmune disease is  
2 selected from the group consisting of rheumatoid arthritis, systemic lupus erythematosus,  
3 multiple sclerosis, and diabetes.

- 1                   42.     The method of claim 39, wherein the cancer is selected from the  
2 group consisting of solid tumors, skin cancer, and lymphoma.
- 1                   43.     The method of claim 39, wherein the cardiovascular disease is  
2 selected from the group consisting of stroke and atherosclerosis.
- 1                   44.     The method of claim 39, wherein the disease of the central nervous  
2 system is a neurodegenerative disease.
- 1                   45.     The method of claim 39, wherein the disease of the skin is selected  
2 from the group consisting of rash, contact dermatitis, and atopic dermatitis.
- 1                   46.     The method of claim 39, wherein the inflammatory bowel disease  
2 is selected from the group consisting of Crohn's disease and ulcerative colitis.
- 1                   47.     A method of inhibiting the transduction of a signal resulting from  
2 the activation of an IL-1R/Toll receptor in a cell, the method comprising introducing into  
3 said cell an inhibitor of the activity or expression of IRAK-4.
- 1                   48.     The method of claim 47, wherein said IL-1R/Toll receptor is  
2 activated by IL-1.
- 1                   49.     The method of claim 47, wherein said inhibitor comprises a  
2 dominant negative form of IRAK-4.
- 1                   50.     The method of claim 49, wherein said dominant negative form of  
2 IRAK-4 comprises a mutation in a lysine residue in the ATP binding pocket.
- 1                   51.     The method of claim 50, wherein said mutation comprises a  
2 substitution of alanine residues for lysine residues within said IRAK-4 at amino acid  
3 positions corresponding to positions 213 and 214 of SEQ ID NO:1.
- 1                   52.     The method of claim 49, wherein said dominant negative form of  
2 IRAK-4 is a truncated form of IRAK-4.
- 1                   53.     The method of claim 52, wherein said truncated form of IRAK-4  
2 consists essentially of amino acids 1 to 191 of SEQ ID NO:1.

54. The method of claim 47, wherein said inhibitor comprises a compound identified using the method of claim 32.

55. The method of claim 45, wherein said inhibitor inhibits activation of at least one transcription factor.

56. The method of claim 53, wherein said transcription factor activates NF $\kappa$ B in said cell.

57. A nonhuman transgenic animal comprising a mutation in an endogenous IRAK-4 gene.

58. The transgenic animal of claim 57, wherein said mutation inactivates said endogenous IRAK-4 gene.

59. The mutation of claim 58, wherein said mutation comprises a deletion of all or part of said endogenous IRAK-4 gene.

60. The transgenic animal of claim 57, wherein said animal is a mouse.

61. An isolated mutant mammalian cell comprising a mutation in an endogenous IRAK-4 gene.

62. The isolated mutant mammalian cell of claim 61, wherein said mutation inactivates said endogenous IRAK-4 gene.